UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/668,196	09/22/2000	Stephen James Russell	18093/1130	9873

7590 11/26/2001

FISH & RICHARDSON P.C. P.A.
60 SOUTH SIXTH STREET
SUITE 3300
MINNEAPOLIS, MN 55402

EXAMINER	
BRUMBACK, BRENDA G	
ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 11/26/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/668,196	Applicant(s) RUSSELL ET AL.	
	Examiner Brenda G. Brumback	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3, 5, 8 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-32 are pending and under examination.

Information Disclosure Statement

2. The Information Disclosure Statements filed 12/22/2000 and 01/05/2001 have been considered. Signed copies are attached hereto. Please Note: the relevance of Document # 3 in the IDS filed 12/22/2000 (U.S. Patent 5,001,692) is not apparent, as this document would seem to pertain to subject matter unrelated to that of the present case. Applicant may wish to review this document for pertinence.

It is noted that there are two references cited in the specification for which there was no submission of the document and which lack complete information regarding the journal of publication (Lorence et al. 1994 and Lorence et al. 1988, cited by author and date only). Applicant is cautioned against the introduction of new matter in responding.

Specification

3. The use of the trademarks ATTENUVAX and PRIORIX has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the

proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

4. Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The present claims recite a method of treating cancer comprising administering a therapeutically effective does of attenuated measles virus to a patient so as to reduce the number of cancer cells in the patient. The claims are indefinite because it is not clear what is encompassed within a "therapeutically effective amount". While the disclosure teaches a reduction in number of cancer cells as a reduction in either size and weight of the tumor, the amount of tumor specific antigen, or the absolute number of cells of at least 10% (see the paragraph bridging pages 8-9), it is not clear that a therapeutically effective amount is equivalent to the amount which reduces the number of cancer cells in a patient or whether it is some other undisclosed amount which is effective for treating cancer.

Claim 5 recites implanting a formulation in proximity to a tumor. "In proximity to" is understood to mean within 1-2 cm of a tumor, as is disclosed at page 7, lines 17-19 of the specification.

Claim 9 recites systemic administration of attenuated measles virus intravenously to a patient through a medical access device. The specification fails to disclose what is encompassed within such a device. Absent such disclosure, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

Claim 10 recites administration of attenuated measles virus in About 10^3 to about 10^{12} and claims 11-15 recite the about 10^3, 10^5, 10^6, 10^7, and 10^8 pfu respectively. The specification fails to disclose the metes and bounds of "about"; thus, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

Claim 20 recites cancer cells selected from melanoma, carcinoma, glioma, myeloma and combinations thereof. It is not clear what is encompassed within the claimed combinations thereof, *i.e.*, are such combinations intended to be a combined population of different cancer cells or a combined cell having characteristics of more than one type of cancer? Clarification and correction are required.

Claims 25 and 27 contain the trademark/trade names ATTENUVAX and PRIORIX . Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the

goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name.

Claim 28 recites the Edmonston Zagreb, Edmonston-Enders, Moraten, and Moraten Berna strains of attenuated measles virus. It is not clear if the terms Edmonston Zagreb, Edmonston Enders, and Moraten Berna denote single or dual viral antigens. For purposes of examination, the claim has been interpreted as encompassing any of the Edmonstron, Edmonston-Zagreb, Enders-Moraten, Moraten, or Berna measles vaccine strains known in the art. Clarification is required.

Claims 29-30 are indefinite for recitation of "a Moraten strain" and "a Edmonston strain". The article "a" connotes that there are plural strains of the Moraten and Edmonston viruses; however, the specification fails to teach the metes and bounds of such strains. Absent such disclosure, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite. The claims are also indefinite for recitation of "non-human cells". The specification fails to teach the metes and bounds of the non-human cells, reciting only a single example (chick embryo cells; see page 13, line 10-13) which can be used to propagate the viruses; thus, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

5. Claims 1-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present,

the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a method of treating cancer comprising administering a therapeutically effective dose of attenuated measles to a patient. Although the claims are indefinite for the reasons outlined previously herein, for purposes of examination herein, the claims have been interpreted as drawn to a method for administering attenuated measles virus to a human patient so as to achieve a beneficial effect on disease manifestation and/or disease progression. As such, the claims encompass the highly experimental and unpredictable field of *in vivo* cancer therapy for humans. Dependent claims recite administration of the virus directly into a tumor or intravenous administration of the virus through a medical access device either continuously or in pulsed doses.

The state of the prior art and the predictability or lack thereof in the art: Smith et al. (Cancer, Vol. 9 No. 6, pages 1211-1218, November-December, 1956) teach that while oncolytic viruses may selectively produce oncolytic effects in cancer cells or tumors, administration of oncolytic viruses is not known to appreciably modify the actual course of disease (see especially page 1217, *Discussion).* Smith et al. further teach that animal models, while providing experimental models of considerable value, are not necessarily predictive of the efficacy of virotherapy in humans due to the differences in specificity of the virus for human and animal cells of other species. Gura (Science 278:1041-1042, November 1997) teaches that the mouse

xenograft model is not predictive of therapeutic efficacy of cancer therapeutics in humans because the xenografted tumors do not behave like naturally occurring tumors in humans (see the entire document and especially page 1041, second column, last full paragraph).

The amount of direction or guidance present and the presence or absence of working examples: The specification discloses inhibition of xenograft tumor formation by infection of tumor cells with an attenuated measles virus; regression of established lymphoma (see Example 1, beginning at page 21), melanoma, breast carcinoma, and glioma xenografts (see Example 2 beginning on page 25) by direct tumor injection with attenuated measles virus ; and regression of myeloma xenografts by intravenous administration of an attenuated measles in a SCID mouse model. There is no guidance in the specification as to how to administer the attenuated measles virus to human cancer patients so as to achieve a therapeutic effect on symptomatology or actual disease progression. There is no guidance as to how to administer the virus in continuous or pulsed doses through a medical access device. All of the working examples are drawn to experimental results in the mouse xenograft model; there is no guidance in the specification as to how to overcome the teachings of unpredictability regarding mouse xenografts that are found in the art.

The breadth of the claims and the quantity of experimentation needed: Because the claims encompass the highly unpredictable field of *in vivo* cancer therapy, because the specification discloses only data generated from mouse xenografts, and because the art teaches that the mouse xenograft model is experimental and not predictive of actual therapeutic efficacy

in humans, it would require undue experimentation by one of skill in the art to be able to practice the claimed invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

a. Claims 1-3 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Bateman et al. (Gene Therapy 6, Suppl 1:S6, Abstract 24, October 1999) or Linardakis et al. (Gene Therapy 6, Suppl 1:S4, Abstract 13, October 1999).

Although indefinite for the reasons outlined *supra*, for purposes of examination herein, the claimed invention has been interpreted as drawn to a method of administering attenuated measles virus to a patient so as to reduce the number of cancer cells in the patient.

Either of Bateman or Linardakis teach that the fusogenic membrane glycoproteins of the measles virus can be administered to a mammal in order to reduce tumor growth and selectively kill cancer cells. Either of Bateman or Linardakis teach that the fusogenic membrane glycoproteins have both cytotoxic and immunostimulatory effects. Although neither Bateman nor Linardakis teach administration of the glycoproteins via an attenuated strain of measles virus,

one of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have administered an attenuated measles virus as a convenient method of administering the fusogenic membrane glycoproteins taught by either of Bateman or Linardakis.

b. Claims 1-25 and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bateman et al. (Cancer Research 60:1492-1497, March 15, 2000; of record in Paper # 5; hereinafter Bateman 2000) in view of Weibel et al. (Archives of Disease in Childhood 48:532-536, 1973).

The claimed invention has been interpreted as drawn to a method of administering a dose of approximately 10^3 to 10^{12} pfu of a vaccine strain of attenuated measles virus, selected from the Moraten line (ATTENUVAX) and the combined MMR vaccine, either intratumorally or intravenously to a patient so as to reduce the number of cancer cells in the patient. Dependent claims recite the cancer as melanoma, among others.

Bateman 2000 teaches administration of the viral fusogenic membrane glycoproteins as a therapeutic for control of tumor growth in a patient (see page 1492, the Abstract). Bateman 2000 teaches that measles virus kills target cells by inducing fusion and that this activity can be exploited therapeutically to kill tumor cells (see page 1492, the last two sentences of the first full paragraph; page 1493, Fig. 1; and pages 1495-1496). Bateman 2000 teaches an exemplary cancer for therapeutic reduction as melanoma (see page 1492, last full paragraph). Bateman

2000 differs from the claimed invention by teaching administration of the glycoproteins via transduction with plasmid DNA, rather than by administration of an attenuated strain of measles.

Weibel et al. teach commercially available preparations of attenuated measles virus either as a monovalent preparation of the Moraten line of measles virus (ATTENUVAX) or as a trivalent preparation of measles, mumps, and rubella (MMR) (see page 532, the abstract and first two paragraphs, and page 533, the second paragraph). Weibel et al. teach administration of the virus preparations as vaccines.

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have used one of the vaccine compositions taught by Weibel et al. as a safe, convenient, and effective means of administering the measles fusogenic glycoproteins taught by Bateman 2000 to be effective therapeutically for control of cancer growth in a patient.

c. Claims 1-17, 20-24, 2628, and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bateman 2000 in view of Usonis et al. (Pediatr Infect Dis J, 18:42-48, 1999).

The claimed invention has been interpreted as drawn to a method of administering a dose of approximately 10^3 to 10^{12} pfu of the Enders Edmonston measles vaccine strain combined with attenuated mumps and rubella viruses (MMR II) , either intratumorally or intravenously to a patient so as to reduce the number of cancer cells in the patient. Dependent claims recite the cancer as melanoma, among others.

Bateman 2000 teaches as outlined above.

Usonis et al. teach two vaccine compositions combining measles, mumps, and rubella live attenuated viruses, the MMR II vaccine comprising the Enders Edmonston measles strain and the PRIORIX vaccine comprising the Schwartz measles strain (see page 42, the abstract and first paragraph of the introduction and page 43, column 2, second from last paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used one of the vaccine compositions taught by Usonis et al. as a safe, convenient, and effective means of administering the measles fusogenic glycoproteins taught by Bateman 2000 to be effective therapeutically for control of cancer growth in a patient.

d. Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Batemen et al. in view of Weibel et al. or Bateman et al. in view of Usonis et al. as applied to claim 1 above, and further in view of Duprex et al. (Journal of Virology 73/11:9568-9575, November 1999.

Either of Batemen et al. in view of Weibel et al. or Bateman et al. in view of Usonis et al. teach a method of treating cancer so as to reduce the number of cancer cells in a patient comprising administering an attenuated strain of measles virus comprising fusogenic membrane glycoproteins, as was set forth *supra*. Neither Batemen et al. in view of Weibel et al. nor Bateman et al. in view of Usonis et al. teach the attenuated measles virus as genetically modified to express a marker polypeptide.

Duprex et al. teach that measles virus can be recombinantly made to express the marker polypeptide, green fluorescent protein. Duprex et al. teach that expression of green fluorescent protein can be used to monitor cellular infection of the measles virus *in vivo* (see page 9568, abstract, and page 9574, last paragraph).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have genetically modified the attenuated measles virus taught by either of Weibel or Usonis to express green fluorescent protein, as taught by Duprex, in order to monitor tumor cell infection and destruction *in vivo*.

e. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over either of Galanis et al. (Gene Therapy 6, Suppl 1:S7, Abstract 28, October 1999) or Russell et al. (Proceedings of the American Association for Cancer Research 41:259, Abstract #1648, March 2000) in view of either Weibel et al. or Usonis et al.

Either of Galanis et al. or Russell et al. teach a method of treating gliomas comprising administering the two fusogenic membrane glycoproteins of measles virus to a patient so as to reduce the number of cancer cells. Neither Galanis et al. nor Russell et al. teach administration of whole attenuated measles virus as a means of administering the glycoproteins.

Either of Weibel et al. or Usonis et al. teach commercially available preparations of attenuated measles virus which are routinely used as vaccine preparations.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered an attenuated measles virus preparation, as described by either of Weibel or Usonis et al., as a convenient and safe means of administering measles fusion membrane glycoproteins for therapy of glioma, as taught by either of Galanis et al. or Russell et al.

Conclusion

7. No claims are allowed.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Bluming et al. (The Lancet, July 10, 1971, 105-106; of record in Paper # 5) teach regression of Burkitts's Lymphoma in a patient after measles virus infection.

Taqi et al. (The Lancet, May 16, 1981: 112) teach regression of Hodgkin's Disease in a patient after measles virus infection.

Adada (Cancer 34:1907-1928, 1974; of record in Paper # 5) teach treatment of human cancer with mumps virus.

Okuno et al. (Biken Journal 21:37-49, 1978) teach treatment of human cancer with mumps virus.

Segni et al. (Giornale di Malattie Infettive e Parassitarie, 44/11:839-846, 1992) teach trivalent measles, mumps, rubella vaccine comprising the Berna strain of measles virus).

Wyde et al. (Vaccine 12/8:715-722, 1994) teach the Edmonston-Zagreb and Enders-Moraten vaccine strains of attenuated measles virus.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

BB
November 20, 2001

Brenda Brumback
Brenda Brumback,
Patent Examiner